Is the Gut Microbiota Disturbed in Chronic Liver Disease?

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By virtue of its anatomical location, blood supply, immunological repertoire, and multiple metabolic roles, the liver is positioned to confront and interact with those microbes, microbial components, and products of microbe-gut interactions that traverse the gut barrier and gain access to the bloodstream.^{1,2} Should the normal homeostatic relationship between the microbiome and the host be disturbed, the ability of the liver to respond be overwhelmed or bypassed, or its response become inappropriate or exaggerated, disease may result.³ This review will focus on the potential role of an altered microbiome in chronic liver disease. Given that the microbiome in health exerts so many important homeostatic effects,^{4,5} the potential impact of an altered microbiome in liver disease can be readily appreciated.

Evidence for a Disturbed Microbiome in Chronic Liver Disease

Small Intestinal Bacterial Overgrowth

By virtue of changes in gut motility and transit, on the one hand, and intestinal permeability, on the other, subjects with chronic liver disease are predisposed to intestinal stasis and bacterial translocation from the gut lumen to portal circulation. Not only has small intestinal bacterial overgrowth (SIBO) been shown to be common across a broad spectrum of chronic liver diseases, but its occurrence is predictive of the severity of liver disease, *per se*, and of such important clinical complications as encephalopathy.^{6,7} Intestinal failure-associated liver disease has been directly linked to SIBO.

Quantitative or Qualitative Changes in Colonic/Fecal Microbiota

In cirrhosis, *Bacteroidetes* are reduced, *Proteobacteria* and *Fusobacteria* increased, *Enterobacteriaceae*, *Veillonellaceae*, and *Streptococcaceae* increased, and *Lachnospiraceae* reduced.⁸

That such findings are not mere epiphenomena but might have some clinical relevance is suggested by associations between microbial population shifts and disease severity, hepatic encephalopathy (HE), liver inflammation, and, given the increased numbers of members of the family *Enterobacteriaceae*, with spontaneous bacterial peritonitis and bacteremia.⁶⁻⁸

What about the involvement of the microbiota in the pathogenesis of nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH)?⁶ First, changes in gut microbiota composition have been demonstrated in obese humans, type 2 diabetes, and metabolic syndrome.^{9,10} Toll-like receptors appear to be important in the pathogenesis of obesity and related inflammation.^{11,12} Changes in the microbiota have also been demonstrated in NAFLD and NASH.¹³ The activation by the microbiota, of proinflammatory cytokines (e.g., tumor necrosis factor α) appears relevant to progression from steatosis to NASH; complex interactions between the inflammasome and the microbiota may also play a role.¹⁴

Regarding alcoholic liver disease, one must recognize the roles that alcohol ingestion alone can play: proliferation of gram-negative bacteria with the consequent production of endotoxin and acetaldehyde, which, in turn, impair the integrity of the intestinal barrier. Not only is the microbiota qualitatively and quantitatively different, in alcoholics,¹⁵ but it is also capable of producing endogenous ethanol from the fermentation of carbohydrates. Other effects of alcohol conspire to increase permeability, promote transfer of endotoxin across the intestinal epithelium, and impair the host immune response.¹⁵

Immunological reactions to the Microbiota

Immune responses involving the microbiota have been invoked in the pathophysiology of a number of liver

Abbreviations: HE, hepatic encephalopathy; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SIBO, small intestinal bacterial overgrowth.

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diseases thought to have an immunological basis; cross-reactivity between bacterial antigens and human tissue components has been proposed as relevant to the pathogenesis of primary sclerosing cholangitis^{16,17} and primary biliary cirrhosis.¹⁸

The Microbiota and Hepatic Carcinogenesis

In experimental animals components of the gut microbiota have been shown to potentiate the hepatic carcinogenic effects of both chemicals and hepatitis viruses, and microbial production of deoxycholic acid has been shown to promote obesity-associated hepatocellular carcinoma.¹⁹

Therapeutic Impact of Modulating the Microbiota

A role for the microbiota in chronic liver disease and its complications or progression can also be inferred from the impact of therapeutic interventions that modify the microbiota.

Antibiotics

Antibiotic therapy, in liver disease, may remove organisms involved in the generation of endotoxin and thereby ameliorate the hyperdynamic circulation thought to contribute to the maintenance of portal hypertension; the ability of antibiotics to not only prevent related infections but also reduce rebleeding rates in variceal hemorrhage may be based on this mechanism.

The antibiotic rifaximin has been shown in high-quality clinical trials to benefit overt and subclinical HE. What is not clear is how rifaximin generates these benefits or, more

precisely, what changes in the microbiota are primarily responsible for these improvements in HE? Interestingly, improvements in cognition in relation to rifaximin therapy in minimal HE were not associated with significant changes in microbial abundance but rather with alterations in gut bacterial linkages and metabolites.²⁰

Probiotics and Prebiotics

Despite a considerable volume of experimental data, the literature on the clinical impact of probiotics in liver disease and its complications is scanty at present. To date, studies of probiotics in liver disease generally have been small in size and their results far from conclusive.

Future Directions

The importance of the microbiome-gut-liver axis has long been recognized clinically and is now being explored and its complexities revealed experimentally. In coming years studies of the microbiome in human disease will rapidly move from purely descriptive to mechanistic and will reveal the precise relevance of specific bugs or bug-derived molecules and their interactions with the host to liver disease and its progression.²¹ ■

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